



## Global Research & Development

September 12, 2000

Documents Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

RE: Draft Guidance for Industry on Chronic Cutaneous Ulcer and Burn Wounds  
Developing Products for Treatment  
Docket No. 00D-1318, 65 Fed. Reg. 39912 (6/28/2000)

Dear Dockets Management:

Pfizer Inc submits these comments on the *Draft Guidance for Industry – Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment*, published in the *Federal Register* on June 28, 2000.

As stated in the Introduction, the document is intended to provide guidance to Sponsors on the development of drugs, biological products, and devices to treat chronic cutaneous ulcer and burn wounds. The guidance, when finalized, will provide recommendations for Sponsors to initiate development programs and a basis for discussions with the appropriate Center at the FDA to clarify requirements to obtain product approval.

We would like to propose that a Public Workshop be held prior to finalizing this guidance. Attendees could include FDA, industry, and the private/public sectors. We believe the contributions obtained at such a workshop would be valuable in preparing the final guidance document.

Historically it has been difficult to measure the efficacy and evaluate the usefulness of drug products for the treatment of chronic cutaneous ulcer and burn wounds. This is a complicated area of research with a long history of development failures. The Draft Guidance provides additional assistance in developing these products and we offer the following observations and comments to further assist in this effort.

### General Comments:

The general difficulty in developing products to treat chronic cutaneous ulcers and burn wounds is recognized in the guidance document. We believe close cooperation and contact between Sponsors and the appropriate Centers should be encouraged. The reason for this is two-fold: first to ensure proper studies and relevant development work are done and second to assist in the general development of criteria for these products.

One difficult aspect of the evaluation of products to treat chronic cutaneous ulcers and burn wounds is the natural tendency of the body to self-repair. We suggest that endpoints and how to measure them still require additional consideration. Follow-up

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periods for each of the respective wounds also merit further consideration to ensure they are realistic and truly distinguish wound healing from transient wound coverage.

We suggest that Quality of Life receive additional consideration under a separate section in the guidance as a desirable consequence of successful treatment of chronic ulcers and burn wounds. Similarly, there are real economic consequences associated with prompt response and successful treatment of chronic cutaneous ulcers and burn wounds. These are areas worth considering in the present health care environment and provide additional justification for the development of products to treat these conditions.

We suggest there should be further consideration of comparator arms, vehicle controls, and the general topic of what are the requirements for a properly controlled study to successfully demonstrate the treatment of chronic cutaneous ulcer and burn wounds. We suggest that "standard care" should be defined and guidance provided as to how this comparator should be developed with regard to the evaluation of new agents for the treatment of chronic cutaneous ulcers and burn wounds.

As noted above, we suggest a Workshop, with participation by CBER, CDRH, CDER, PhRMA/Industry, and the private/public sectors be organized after the comments to this draft guidance have been incorporated and the guidance is ready for final review before issuance. A Workshop would permit direct input and a cooperative atmosphere to ensure input from all affected parties is included in the guidance document.

## **Specific Comments on the Guidance**

### **Section I., (Introduction)**

- Arteriothrombotic ulcers are addressed under IV.C.1 (Ulcer Classification) ("arterial insufficiency" – p. 9) and should also be included here. (p.1)

### **Section II.A., (General Considerations)**

- Regarding the statement that "Separate safety and efficacy data should be submitted..." we suggest that the word, "Separate" be deleted – the wording suggests that pooled data could not be used. (p.2)

### **Section II.B.1., (Incidence of Complete Wound Closure)**

- Regarding the definition of "complete closure" in the first paragraph, we suggest the following definition: "Complete closure is defined as complete re-epithelization without drainage or dressing. It is however acknowledged that dressings could be used to protect the newly formed skin." We note that a prespecified time for endpoint measurement will be product-specific and each drug product will be different. (p. 2)
- The FDA (paragraph 2, line 3) states that follow-up after complete closure should be continued for at least 3 months. It may be appropriate for the FDA to provide guidance on the length of time needed for clinical trials in different ulcer types. We suggest the FDA consider defining what a wound is – one single ulcer or an area of ulceration on the leg, which could include multiple ulcers? (p. 2)

- In the first paragraph, eighth line, we suggest clarification is needed as to whether the “control arm” refers to the standard care alone and/or the vehicle plus standard care. (p.2)
- In the second paragraph, we suggest the phrase “durability of the effect” (durability of the closure) be defined. Is it disruption of reepithelization/breakdown of the ulcer skin? Under what conditions (we suggest the FDA consider defining the conditions) is the durability of effect to be measured only by the investigator’s assessment? (p.2)
- In light of the statement on page 2 regarding the fact that measurement of partial healing could not be used as primary efficacy evidence, we believe further discussion is merited regarding when partial healing may facilitate a surgical closure claim. (p. 3)

**Section II.B.2., (Accelerated Wound Closure)**

- Regarding accurate measurement of wound size:  
We suggest the FDA indicate in the guidance acceptable methods for measurement of ulcer or wound size. (p. 3)
- Regarding reduction in the size of the wound:  
We suggest that the FDA provide guidance on evaluation of wound size reduction from a statistical perspective. We believe Gilman’s equation, mean adjusted rate of healing, is appropriate. (p. 3)
- We believe the first six lines of the second paragraph require further clarification. Is the FDA suggesting that the incidence of closure is a more important outcome than time to healing? And if an increased time to healing claim is targeted, should the Sponsor compare data at same incidence of closure? (p.3)
- The end of the second paragraph states that a claim of *improved incidence of closure* should not be supplemented by an additional claim of *accelerated wound closure*. We suggest that “should not be supplemented” be replaced by “does not necessarily need to be supplemented.” Otherwise you would exclude the possibility of having a drug increasing the incidence of closure but also decreasing significantly the time to closure. Is it possible to support the two claims with a conditional analysis of time to healing? (p.3)

**Section II.B.3., (Facilitation of Surgical Closure)**

- For the claim of “facilitates surgical closure”, we suggest that specific endpoints (e.g. the “wound size”) be included. Establishment of acceptable endpoints will be difficult due to the subjective nature of this claim. (p.4)
- The last paragraph in this subsection refers to evaluating “healing outcomes such as durability, functionality, and cosmetic appearance, including scarring.” We suggest that guidance be provided on how to accomplish these healing outcomes measurements (i.e. use of scores, imaging, etc.). It would also be desirable to include examples of validated assessment tools. (p. 4)

**Section II.B.4., (Improved Quality of Healing)**

- We note that many people desire less scarring at sites other than the face, and suggest a claim such as "improved cosmesis" for treatment of such sites (such as an unsightly leg ulcer). We suggest that an "improved cosmesis" claim be added to the "improved incidence of closure" type of claim as described in section II.B.2. (Accelerated Wound Closure). (p. 4)
- The first paragraph in this subsection states, "...it is important to consider whether a reliable assessment tool exists, or can be developed...." We suggest that further discussion is merited regarding this topic. (p. 4)

**Section III.A., (Animal Models for Wounds)**

- This subsection notes that "multiple animal models are typically used to assess activity of wound healing agents." This suggests that several animal models should be/will be used to demonstrate different types of activity. We suggest that the guidance state: "There are several animal models that can be used to assess specific activities of the product." This would then be followed by: "The following are examples of animal models that can be used." (p. 6)

**Section III.B., (Biodistribution and Pharmacokinetic Studies)**

- We recognize that wound healing agents have the potential to alter the PK profile and result in product accumulation with repeated dosing. However, use of appropriate excipients may prevent this type of situation and we therefore suggest that something be added to the subsection to note the ability of the formulation excipients to alter the PK characteristics. (p.6)
- We suggest a change in wording for the following language currently near the end of the paragraph: "...and for biological products, target receptor levels, contribute..." The suggested change is as follows: "...and for biological products that interact with target receptors, receptor levels contribute.." (p. 6)

**Section III.C., (Toxicity Studies)**

- Photoirritation testing is not included in the guidance. We believe this testing is an important requirement prior to exposure to patients or even healthy volunteers, especially when the product remains at the wound site and is negligibly absorbed through the wound bed. (p. 7)
- The need for long term toxicology studies should also be discussed in light of the systemic exposure for the topicals. This discussion should consider both the metabolic profile of the drug and results in systemic exposure. We suggest that the omission of long term toxicology studies could be justified where the systemic exposure (as defined by the AUC) is sufficiently reduced in animals compared with human exposure. We also suggest that as for the PK studies, that the subcutaneous route could be considered as the most representative route for the toxicology studies. (p. 7)
- With regard to conducting carcinogenicity studies for drugs intended for chronic ulcers, we suggest the guidance emphasize the topical route of administration. (p. 7)

- This subsection discusses current unresolved issues regarding the carcinogenic and tumorigenic potential of wound healing products. One such issue that is discussed addresses the potential for a test agent to stimulate the growth of normal and/or malignant cells that express the receptor for the agent. Please clarify whether this refers to biologicals only or whether it should be a separate paragraph covering all products. (p. 7)

#### **Section IV.A., (Absorption Studies)**

- The first paragraph states that "phase 1 evaluations should include quantitation of absorption through the wound." We suggest that "phase 1" be replaced by "early clinical" so that this type of evaluation is not only restricted to phase 1 clinical trials. (p. 8)
- The first paragraph also notes that relatively little (<1%) absorption typically occurs from chronic ulcer sites. We suggest that the last sentence of this paragraph be replaced with the following: "When little absorption occurs at the ulcer sites, sensitive assays against serum background should be performed. It is particularly the case with growth factors where even small amounts of drug absorbed from the ulcer can be clinically significant as they are active *in vitro* at nanogram concentrations. The sensitivity of the assay should be determined based on the expected systemic exposure in humans." (p.8)
- The second paragraph notes several factors that influence systemic dose when products are absorbed from the wound bed. We suggest that the following additional factors be added: systemic distribution and clearance. We note that in this and the following paragraphs, only systemic assessment is mentioned. There is also the need to mention the local PK/PD, i.e. use of wound fluid and biopsies. (p. 8)

#### **Section IV.C.2., (p. 9; Wound Size) and Section IV.E.1.a., (p. 12; Debridement)**

- Page 9 states that quantitative assessments of wound size are made before and after debridement. However, on page 12 it is stated that "to avoid bias and confounding of treatment effect," the ulcer should be evaluated after debridement. We suggest that p. 9 include the post ulcer debridement recommendation made on p. 12.

#### **Section IV.C.3., (Wound Imaging)**

- It is stated that photos should be taken to corroborate the direct measurements. We suggest that tracing be included as an alternative means of capturing the photographic record, allowing for variability of tracing quality across sites. (p. 10)
- This subsection suggests that imaging procedures are needed to confirm the CRF measurements made by the investigators. We believe that imaging/photo procedures are more accurate and powerful tools. We suggest that the CRF measurements should be acceptable when imaging/photo procedures are not used or are not available. (p. 10)

#### **Section IV.C.4., (Infection)**

- It is stated that biopsies are generally preferred to determine if a wound is infected or merely colonized and to guide appropriate antimicrobial therapy. Biopsies may be preferred in particular centers, but it is more a question of common practice. Therefore, we suggest that the last sentence be rephrased as follows: "In common clinical practice, this method is preferred..." (p. 10)

#### **Section IV.D.1., (Chronic Cutaneous Ulcers)**

- The draft guidance states that variability can be reduced by evaluating ulcers of only a certain size, but with the potential that this would impact the product label. This impact, and the possible impact of the incorporation of this idea in early studies, merit further discussion. We suggest that the measure of healing should be established and the rate of healing should be independent of initial size. (p. 11)

#### **Section IV.E., (Standard Care)**

- In the fifth line of the first paragraph of this section, we suggest that in the phrase "...participating centers agree to use the same procedures." the words "agree to" be deleted. (pgs. 11-12)

#### **Section IV.E.1.d., (Infection Control)**

- We suggest that in the second paragraph, which discusses infection of ulcers, that a reference to section IV.C.4. should be added on how to assess infection. (p. 14)
- With regard to the use of antimicrobial therapy (third paragraph), if topical treatment and then topical antimicrobial is used, then patients should be withdrawn. If systemic antimicrobials are used, then inclusion of this subset in the analysis needs to be decided prospectively. (p. 14)

#### **Section IV.F.1., (Effects of the Product on the Wound)**

- "and/or increase in ulcer size" is noted as a deterioration of a target wound. However, we note that it is part of the natural process of wound healing for the ulcers to firstly increase and then decrease in size. Therefore, we suggest the text should read "...and/or a clinically significant increase in ulcer size." (p. 15)
- There is no mention of the possible systemic effect of the product. We suggest that this should be added. (p. 15)

#### **Section IV.G.2., (Comparator Arms)**

- This subsection describes work required to evaluate the safety and effect of the vehicle. In the second sentence ("To evaluate the safety and effect of the vehicle..."), what does "effect of the vehicle" mean? Safety of the vehicle has to be demonstrated, but this sentence suggests its potential efficacy would be examined. We suggest the sentence could be rephrased as follows: "Safety of the vehicle should be assessed as late as in Phase 2. This should be done by having a study arm treated with standard care alone versus standard care plus vehicle." Is this sufficient or does negative efficacy also need to be demonstrated? We suggest further discussion is needed regarding this topic. (p. 16)

#### **Section IV.G.3., (Masking)**

- The fourth line of this subsection contains the following: "...to establish whether the vehicle has an effect on healing." We suggest adding the word "adverse" before "effect" to emphasize that it is the vehicle safety that is being evaluated. Does this section imply that equivalence trials would be needed to show that the vehicle plus standard care are not different from standard care alone? (p. 16)
- In line 6, which states "especially in some devices...", we suggest that the following wording be added: "or where the test substance is colored or alters physical characteristics of the formulation," (p. 16)

**Section IV.H., pages 16-17 (Statistical Considerations Specific for Wound Product Trials)**

General comments regarding "Statistical Considerations":

- We suggest the center should be considered as a factor in analysis in addition to time to healing data.
- Should the danger of over-dispersion be spelled out if the center is not included as a factor in a logistic regression analysis of proportion of ulcers healed/not healed?
- For Cox Proportional Hazards model – we suggest it should emphasize that the assumption of proportional hazards should be reasonable to apply this model.
- Growth curve models for rate of healing. Does it refer to methods for the analysis of repeated measures? Much of the repeated measures methodology have been developed from growth curve models and some of the literature still refers to the methods as growth curve methods (e.g. the classic reference of Laird & Ware, Biometrics 1982). We request that this be clarified.
- We suggest using ANOVA methods of analyzing change in size.
- Missing values and imputation – it is not straightforward to account for missingness in the analysis. Methods usually rely on the type of missingness – e.g. missing at random, etc. We suggest there should be specific guidelines/recommendations on methods.
- Regarding missing values, the draft guidance states "the worst case outcome can be used to determine the maximal effect of missing values." This analysis is highly biased, but that is not stated. We suggest that the guidance recommend appropriate analytical techniques to assess the impact of missing values on the data and REDUCE bias should be used.
- We would like to solicit the FDA's views on using intention to treat methods for missing values.
- We suggest the recommendation in the section on covariates about continuous covariates in preference to cut-points is arguable. Clearly, cut-points have to be pre-defined but at least if used, one is not required to make the assumption that the covariate effect is linear on the appropriate scale, which you do with a continuous covariate. We suggest that sweeping generalities should be avoided regarding continuous vs. dichotomized, etc. It would be more helpful if the guidance had specific information concerning covariates that had in the past been shown to be related to response, what they were, and how they were related (e.g. linearly, etc.).
- There is no mention of how to analyze data, which are scores e.g. wound improvement scores. This would be useful.

- The draft guidelines do not provide much information on measurements or endpoints. We believe this is rather crucial, especially as they discuss various labeling claims in much detail. It would be useful to link each claim with a specific endpoint.

**Attachment, pages 18-19 (Wound Product Quality Microbiology)**

- The requirement that "the final formulation...should be sterile..." requires clarification. Does it refer to the commercial formulation only? For early clinical trials, would a sterile formulation be recommended? We suggest that a low bioburden limit (such as the 10 cfu/g as mentioned in the last paragraph of the Attachment) would be acceptable even for early clinical formulations if sterility has not yet been achieved.
- Preservative content is discussed, the Attachment stating for preservative "with amount of preservative less than or equal to the minimum amount..." We suggest that "less than or equal to" be replaced by "less than AND equal to". The preservative concentration in the product should not exceed the minimum quantity required to provide the intended effect (in line with USP 24 guidance). Thus the microbial challenge test should be performed at two concentrations – the concentration in the product and a lower concentration (the latter demonstrating preservative failure).
- References to USP 23 should be updated to USP 24.

We thank you for this opportunity to comment on the *Draft Guidance for Industry – Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment*. We look forward to working with CBER, CDRH, and CDER on finalization of the draft guidance document, perhaps participating in a Workshop to facilitate a final review and discussion of the guidance document before it is issued.

Sincerely,



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Senior Vice President  
Pfizer Global Research and Development  
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